REMARKS

This amendment is responsive to the Office Action mailed November 15, 2007. Previously, claims 1, 3, 6, 8-11, 17, 50, and 52-67 were pending and under consideration. In the present paper, claims 1 and 50 are amended. Thus, following entry of the present amendment, claims 1, 3, 6, 8-11, 17, 50, and 52-67 remain pending and under consideration.

Applicants acknowledge the PTO's withdrawal of the rejections under 35 U.S.C. § 112, 2nd paragraph and double patenting and kindly thank the PTO for the same. The PTO's objections and rejections to the pending claims are addressed in detail below.

I. The Amendments to the Claims

In the present paper, claims 1 and 50 are amended. As the amendments to the claims are fully supported by the application as filed, no new matter is presented by the present amendment to the claims.

Specific support for the amendment to claims 1 and 50 may be found, for example, in the specification at page 3, paragraph 0026, page 16, paragraph 0078, and in claims 1, 12, 20, 25, 42, and 45 as filed.

As the amendments to the claims are fully supported by the application as filed, they present no new matter. Accordingly, entry of the present amendment to the claims is hereby respectfully requested under 37 C.F.R. § 1.111.

II. Priority

The Examiner alleges that the disclosure of the prior-filed Application No. 60/475,402 (the '402 application) and Application No. 10/684,440 (the '440 application) fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims in the instant application. The Examiner asserts that the instant application is entitled to benefit of priority to only International Patent Application No. PCT/US04/14540 (the '540 application), having a filing date of June 2, 2004. Without acquiescing to the Examiner's conclusion, Applicants respectfully submit that the present application is entitled at least to the priority date of the '540 application.

III. The Objections of Claims 52 and 53 Should Be Withdrawn

Claims 52 and 53 are objected to as being dependent on a rejected base claim, but the PTO acknowledges that the claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants

respectfully submit that the PTO's objection is obviated by the patentability of the base claim, claim 50, as discussed in detail below. Accordingly, Applicants respectfully request withdrawal of the objection.

IV. The Rejection of Claims 1, 3, and 17 as Anticipated Should Be Withdrawn

Claims 1, 3, and 17 stand rejected under 35 U.S.C § 102(b) as allegedly being anticipated by Cai *et al.* (International Patent Publication No. WO 2004/108916). In particular, the PTO contends that Cai *et al.* teaches an antisense oligonucleotide of 26 nucleobases in length that is 100% complementary to a portion of nucleotides 12380-13493 of SEQ ID NO: 4.

Applicants respectfully submit that the rejection is moot in view of the amendments to the claims. As amended, claim 1 recites an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4. Thus, when each nucleotide of the oligonucleotide of Cai *et al.* is considered in calculating the percentage of complementarity, the oligonucleotide is 92.3% (24 of 26 bp) complementary to SEQ ID NO.: 4. As the oligonucleotide of Cai *et al.* is less than 94% identical to this sequence, it does not teach this element of claim 1. As such, Cai *et al.* cannot anticipate claim 1 as amended, or claims 3 and 17 depending therefrom, since it fails to teach each and every element of the invention as presently claimed. *See Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 68 USPQ2d 185 (Fed. Cir. 2003).

Accordingly, Applicants assert that the rejection of claims 1, 3, and 17 as anticipated by Cai *et al.* is moot in view of the amendments to the claims and therefore request its withdrawal.

V. The Rejection of Claims 1, 3, 6, 8-11, 17, 54-60, and 62-67 as Obvious Should Be Withdrawn

Claims 1, 3, 6, 8-11, 17, 54-60, and 62-67 are rejected under 35 U.S.C § 103 as allegedly obvious. Applicants respectfully submit that the references cited by the PTO, whether considered alone or in combination, fail to teach or suggest each and every element of the invention recited by the pending claims of the present application. Thus, Applicants respectfully submit that the claims are not obvious over the combination of references cited by the PTO, as discussed in detail below.

A. The Legal Standard

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), the Supreme Court enunciated the standard for evaluating obviousness of a claimed invention. "[T]he scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." *Graham,* 383 U.S. at 17-18.

The Supreme Court recently articulated in *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727 (2007) the proper analysis for ascertaining the differences between the prior art and claimed invention under the *Graham* test. According to the Supreme Court, "it will be necessary for a court to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue," *Id.* at 1740-41. The Supreme Court further emphasized that "this analysis should be made explicit." *Id.* at 1741, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Moreover, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). In addition, one of ordinary skill in the art must have a reasonable expectation of success in achieving the claimed invention. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

B. The Cited References Do Not Teach or Suggest All Claim Limitations of Claims 1, 3, 6, 8-11, 17, 54-60, and 62-67

Claims 1, 3, 6, 8-11, 17, 54-60, and 62-67 stand rejected under 35 U.S.C § 103(a) as allegedly obvious Ruoy *et al.* (International Patent Publication No. WO 99/65241) in view of Morishita *et al.* (*Circulation*, 1998, 98:1898-1904) and Baracchini *et al.* (U.S. Patent No. 5,801,154).

None of the cited references, either alone or in combination, teach or suggest an antisense compound at least 90% or 94% complementary to nucleotides 12380-13493 of SEQ ID NO: 4. Ruoy *et al.* neither teaches nor suggests that an antisense compound should be targeted to any particular region of the coding region of apolipoprotein(a). Further,

Morishita *et al.* teaches that ribozymes that cleave apolipoprotein (a) mRNA are specifically targeted to kringle 4 protein domain located at position +151 of apolipoprotein (a) mRNA, and less effectively at positions +120 and +164 (at page 1900, 1st paragraph under the heading "Results"). According to Morishita *et al.* the three target sequences represent possible ribozyme catalysis sites within the kringle 4 protein domain.

Morishita *et al.* does not teach, however, that nucleotides 12380-13493 of SEQ ID NO: 4 should be targeted. Rather, Morishita *et al.* discloses that the antisense technology may not be useful in inhibiting apolipoprotein (a) expression because "it is difficult to select antisense sequences around ATG sites that are most commonly and effectively used as antisense sequences" (at page 1903, 2nd paragraph). Thus, to the extent Morishita *et al.* discusses use of antisense technology to inhibit apolipoprotein (a) expression, it suggests that sequences around ATG sites should be targeted for effective inhibition. Morishita *et al.* does not teach or suggest that nucleotides 12380-13493 of SEQ ID NO: 4 should be targeted, or even suggest that there are kringle 4 protein domains within nucleotides 12380-13493 of SEQ ID NO: 4. Therefore, Morishita *et al.* cannot remedy the deficiency of Ruoy *et al.*

Moreover, Baracchini *et al.* does not teach or suggest anything regarding antisense modulation of apolipoprotein(a) expression. Rather, Baracchini *et al.* merely provides general teaching that antisense compounds can be targeted to the coding region of a gene and teaches generally chemical modifications of oligonucleotides. Baracchini *et al.* does not teach or suggest that nucleotides 12380-13493 of SEQ ID NO: 4 should be targeted. As such, Baracchini *et al.* cannot cure the deficiencies of Ruoy *et al.* and Morishita *et al.* discussed above. Therefore, the combination of references, when considered as a whole, fails to teach or suggest each and every element of the invention as presently claimed.

Furthermore, the PTO has not identified an explicit reason to combine the elements of Ruoy *et al.*, Morishita *et al.*, and Baracchini *et al.* in the fashion claimed in the present application. In particular, although the PTO contends that one skilled in the art would have been motivated to target the coding region of apolipoprotein(a), as allegedly taught by Morishita *et al.* and Baracchini *et al.*, with the antisense oligonucleotides of Ruoy *et al.*, the PTO has not provided an explicit reason why nucleotides 12380-13493, out of the entire coding sequence of apolipoprotein(a), should be targeted. Contrary to the PTO's assertion, Morishita *et al.* merely discloses specific targeting of the kringle 4 protein domain located at certain positions in the coding region that are cleavable by ribozymes. Nowhere does Morishita *et al.* provide any reason why nucleotides 12380-13493 of SEQ ID NO: 4 should be targeted with antisense compounds. Further, Baracchini *et al.* merely provides general

teaching that antisense compounds can be targeted to the coding region of a gene and thus cannot cure the deficiencies of Ruoy *et al.* and Morishita *et al.*. As such, the PTO has failed to provide a reason why the teaching of Morishita *et al.*, Ruoy *et al.*, and Baracchini *et al.* should be modified to achieve the presently claimed invention. According to the Supreme Court, the PTO cannot establish that the present claims are obvious over the references without making such analysis explicit. *KSR* at 1740-41.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C § 103(a) be withdrawn.

VI. The Rejection of Claims 1, 3, 6, 8-11, 17, 50, and 52-56 as Failing to Comply with the Written Description Requirement Should Be Withdrawn

Claims 1, 3, 6, 8-11, 17, 50, and 52-56 are rejected under 35 U.S.C § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully submit that the rejection is obviated by the deletion of "a portion of" language in claims 1 and 50. As amended, claim 1 recites an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4, and claim 50 recites an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 90% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4 and wherein the antisense compound comprises at least 8 contiguous nucleobases of SEQ ID NO: 87.

With regard to written description of claimed ranges, an application need not describe the claimed range *in haec verba* to provide an adequate written description of the range. *See In re Wertheim*, 191 USPQ 90 (C.C.P.A. 1976) and *Ralston Purina Co v. Far-Mar-Co., Inc.*, 227 USPQ 177 (Fed. Cir. 1985). Rather, the written description analysis must take into account what one skilled in the art would consider inherently supported in the original disclosure. *See id.* For example, an application's description of a range of "25% to 60%" and "36%" is sufficient to support a claim reciting a range "between 35% and 60%." *See Wertheim*, 191 USPQ at 98.

Applicants respectfully submit that the present application provides adequate written description support for the claimed ranges of "at least 90% complementary" and "at least 94% complementary." Specific support can be found, for example, at page 10, lines 5-13, and page 11, line 13 of the specification as filed. Thus, "at least 90% complementary" is

explicitly taught by the specification. Further, as the claimed range need not be described *in haec verba* to provide an adequate written description of the range, Applicants respectfully submit that "at least 90%" and "about 94%" disclosed in the specification provide an adequate written description of the range of "at least 94% complementary." *See Wertheim*, 191 USPQ at 98.

A range of at least 90% and at least 94% complementary corresponds to a range of 90 to 100% or 94 to 100% complementary, respectively. The specification at page 11, lines 11-15 describes compounds having sequence complementarity of about 90%, about 92%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%. As such, the specification provides support for numerous individual species within the claimed ranges of at least 90% and at least 94%. Therefore, the disclosure of the application reasonably conveys to the skilled artisan that Applicants were in possession of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983). Applicants therefore respectfully submit that the present application provides adequate support for the claimed ranges.

Moreover, the specification provides compounds that are at least 90% or 94% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4. Exemplary compounds can be found, for example, at page 107 (Table 1, SEQ ID NOs: 36, 37, and 38), and at page 127 (Table 7, SEQ ID NOs: 86-96). Thus, Applicants provide numerous representative species of compounds that are at least 90% or 94% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4 that would lead one skilled in the art to recognize that the inventors were in possession of the claimed genus. As such, Applicants respectfully submit that the specification provides an adequate written description of claims 1 and 50, and each of the claims depending therefrom.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C § 112, first paragraph be withdrawn.

VII. The Rejection of Claims 1, 3, 17, and 50 as Anticipated Should Be Withdrawn

Claims 1, 3, 17, and 50 stand rejected under 35 U.S.C § 102(b) as allegedly being anticipated by Mittman (U.S. Application No. 2003/0104410 A1). In particular, the PTO contends that Mittman teaches an antisense oligonucleotide of 25 nucleobases in length wherein the antisense compound comprises 13 contiguous nucleotides of SEQ ID NO: 87, and therefore, is 100% complementary to a portion of nucleotides 12380-13493 of SEQ ID NO: 4.

Applicants respectfully submit that the rejection is obviated by the deletion of "a portion of" language in claims 1 and 50. As amended, claim 1 recites an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4, and claim 50 recites an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 90% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4 and wherein the antisense compound comprises at least 8 contiguous nucleobases of SEQ ID NO: 87.

Thus, when each nucleotide of the oligonucleotide of Mittman is considered in calculating the percentage of complementarity, the oligonucleotide is 64% (16 of 25 bp) complementary to SEQ ID NO.: 4. As the oligonucleotide of Mittman is less than 90% or 94% complementary to this sequence, it does not teach this element of claims 1 and 50. As such, Mittman cannot anticipate claims 1 and 50 as amended, or claims 3 and 17 depending therefrom, since it fails to teach each and every element of the invention as presently claimed. *See Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 68 USPQ2d 185 (Fed. Cir. 2003).

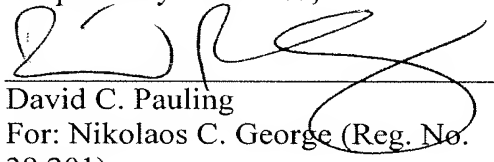
Accordingly, Applicants respectfully submit that the rejection of claims 1, 3, 17, and 50 as anticipated by Mittman is moot in view of the amendments to the claims and therefore request its withdrawal.

CONCLUSION

In light of the above remarks, Applicants respectfully request that the PTO reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (650) 739-3949, if a telephone call could help resolve any issues.

Respectfully submitted,

Date: February 15, 2008



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David C. Pauling (Reg. No.)
For: Nikolaos C. George (Reg. No. 39,201)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939